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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,951	01/11/2002	Leonid Beigelman	MBHB00,716-D (RPI No. 600)	7085

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EXAMINER

LEWIS, PATRICK T

ART UNIT PAPER NUMBER

1623

DATE MAILED: 08/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/043,951

Applicant(s)

BEIGELMAN ET AL.

Examiner

Patrick T. Lewis

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 June 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-45 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-45 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_                      6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election with traverse of the species adenosine in Paper No. 11 dated June 12, 2003 is acknowledged. The traversal is on the ground(s) that "the method of the claims is essentially the same, regardless of what nucleoside is employed, and thus the Examiner's search would be limited to such method". This is found persuasive. The requirement dated April 7, 2003 has been WITHDRAWN.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "selectively desilylating the product from (c)" renders all claims in which it appears indefinite. Applicant has failed to particularly and distinctly set forth which position(s) of the nucleoside is subjected to desilylation. Without further clarification one of ordinary skill in the art would not be fully apprised of the metes and bounds of the instantly claimed methods.

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-8, 11-18, and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. J. Org. Chem., 1999, Vol. 64, pages 747-754 (Tang).

Tang discloses a method for the synthesis of phosphoramidite derivatives of 2'-C- $\beta$ -methylcytidine within the scope of the instantly claimed method (page 748, Scheme 1). The method of Tang comprises a) introduction of a nucleic base-protected nucleoside; b) 5',3'-cyclic silyl protection of the nucleoside using *t*-Bu<sub>2</sub>SiCl<sub>2</sub>; c) protection of the 2'-hydroxyl using *t*-BuMe<sub>2</sub>SiOTf; d) selective removal of the 5',3'-cyclic silyl protective group using HF-pyridine; e) protection of the 5'-hydroxyl using DMTrCl; and f) the introduction of a 3'-O-(2-cyanoethyl-N,N-diisopropylphosphoramidite) moiety.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Tang et al. J. Org. Chem., 1999, Vol. 64, pages 747-754 (Tang) and Usman et al. J. Am. Chem. Soc. 1987, Vol. 109, pages 7845-7854 (Usman).

Claims 1-45 are drawn to a method for synthesizing a 2'-O-silyl-nucleoside phosphoramidite comprising:

- a) introducing a 5',3'-cyclic silyl protecting group to a nucleoside;
- b) introducing a 2'-O-silyl protecting group to the product from (a);
- c) selectively desilylating the product from (b);

- d) introducing a 5'-hydroxyl protecting group to the product from (c);
- e) introducing a phosphoramidite moiety at the 3'-position of the product from (d),
- and
- f) optionally introducing a nucleic acid base protection group if necessary to the nucleoside before step (a) or after step (b).

Tang teaches a method for the synthesis of phosphoramidite derivatives of 2'-C- $\beta$ -methylcytidine (page 748, Scheme 1). The method of Tang comprises a) introduction of a nucleic base-protected nucleoside; b) 5',3'-cyclic silyl protection of the nucleoside using *t*-Bu<sub>2</sub>SiCl<sub>2</sub>; c) protection of the 2'-hydroxyl using *t*-BuMe<sub>2</sub>SiOTf; d) selective removal of the 5',3'-cyclic silyl protective group using HF-pyridine; e) protection of the 5'-hydroxyl using DMTrCl; and f) the introduction of a 3'-O-(2-cyanoethyl-N,N-diisopropylphosphoramidite) moiety.

Tang differs from the instantly claimed invention in that: 1) Tang does not teach the protection of the nucleic base after step (b); 2) Tang only teaches the use of methylcytidine as the nucleoside; and 3) Tang does not teach the introduction of a 2'-O-triisopropylsilyloxymethyl protecting group.

Usman teaches the automated chemical synthesis of oligonucleotides using 2'-O-silylated ribonucleoside 3'-O-phosphoramidites. Usman teaches using both TBDMS and TIPS as the 2'-O-protective group for ribonucleoside phosphoramidites (page 7846, Scheme I). Usman further teaches using various nucleic acid bases.

It would have been obvious to one of ordinary skill in the art at the time of the invention to protect the nucleic acid base after step (b) since Tang teaches of the steps

employed in the instantly claimed method including protection of nucleic acid base. Merely reversing the order of the steps of a multi-step process does not impart patentability when no unexpected result is obtained. *Ex parte Rubin* (POBA 1959) 128 USPQ 440; *Cohn v. Comr. Pats.* (DCDC 1966) 251 Fsupp 437, 148 USPQ 486. The practice of the instantly claimed invention using a nucleic acid base moiety other than methylcytidine and the selection of appropriate silyl-protecting groups is seen to be within the purview of the skilled artisan as demonstrated by Usman. One would have been motivated to do so in order to produce analogues useful to regulate gene expression by antisense or ribozyme cleavage approaches.

### ***Conclusion***

10. Claims 1-45 are pending. Claims 1-45 are rejected. No claims are allowed.

### ***Contacts***

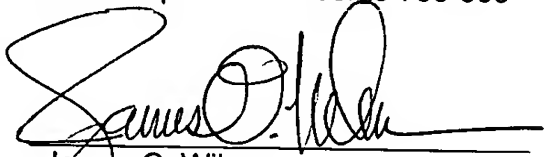
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 10:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD  
Examiner  
Art Unit 1623

ptl  
August 19, 2003



James O. Wilson  
Supervisory Patent Examiner  
Technology Center 1600